



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM:

To: Julie Chao

From: Autumn Metzger, M.S.

AM 8/12/14

Date: 8/12/14

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD

DP barcode: 420896

Decision no.: 491741

Submission no: 953017

Action code: R340

Product Name: Activyl For Dogs and Puppies

EPA Reg. No or File Symbol: 773-94

Formulation Type: Spot-on

Ingredients statement from the label with PC codes included:

Indoxacarb, 067710

Application rate(s) of product and each active ingredient: (based on the highest weights of each weight bracket i.e. the most conservative weights)

Labeled & tested dose is ≥ 15 mg/kg BW

Tested dose is marketed vial (.51 ml/.77 ml/1.54 ml/3.08 ml/4.62 ml) used on appropriate size dog

I. Action Requested:

The purpose of MRID 49349101 is to support claims against cat fleas on dogs after antibacterial shampoo treatment

The purpose of MRID 49349102 is to support claims that is effective against cat flea feeding within 3 hours of application and stopping cat flea feeding within 6 hours of application

II. Background: Currently registered dog spot on looking for additional claims.

III. MRID Summary: (primary review is attached)

MRID 49349101. Liebenberg, J.E., Impact of Antibacterial Shampooing on the Efficacy of Activyl® (Indoxacarb) Topical Treatment against Cat Flea (*Ctenocephalides felis*) Infestations on Dogs under Laboratory Conditions. Dec. 13, 2013.

(1) Not GLP

(2) Study Design (from the primary review):

Test Material(s):

Treatments followed the dose rates as set out below.

| Study groups | Sample size | Treatment | Active ingredient | Weight range | Dose |
|--------------|-------------|-----------|-------------------|--------------------|---------|
| 2 & 3 | 6 | Activyl® | Indoxacarb | > 6.6 kg to 10 kg | 0.77 mL |
| | | | | > 10.1 kg to 20 kg | 1.54 mL |
| | | | | > 20.1 kg to 40 kg | 3.08 mL |

List the treatments including untreated control (express application rate as g/m²):

Eighteen healthy, mongrel dogs, weighing 8.50 kg to 21.03 kg on Day -2, were studied in this parallel group design, randomized, single center, blinded, and controlled efficacy study. On Day -2, the 18 dogs included were ranked within gender in descending order of individual pretreatment live flea counts and subsequently grouped into blocks of three dogs each: Group 1, negative control; Group 2, IVP treated (Activyl® on Day 0) and shampooed on Days 9 and 23; and Group 3, IVP treated (Activyl® on Day 0), but not shampooed.

Hair lengths on the dogs averaged 19.79 mm in Group 1, 21.92 mm in Group 2, and 18.33 mm in Group 3.

Following administration, animals from all groups were observed approximately hourly for four hours for adverse reactions to treatment.

Flea infestations were performed with 100 adult, unfed *Ctenocephalides felis* (European origin) placed on each dog on Day -2 and then weekly from Days 7 to 28. Fleas were removed and counted 48± 2 hours post-infestation except for Day -2 infestation where the assessment was performed on Day 2.

Shampooing:

All dogs were shampooed with an antibacterial shampoo (Virbac KetoChlor®) in a designated area as follows:

After the flea counts had been completed, the dogs were soaked with warm tap water. The shampoo was applied all over the dog, including the head, and the animals were lathered manually, after which the shampoo was rinsed off with tap water. The dogs were dried sufficiently using a blow-dryer before returning them to their cages. The volume of shampoo applied and the time of shampooing were recorded. The shampooing was done by a non-blinded person to ensure that the negative control group was shampooed before the treated group.

(3) Results:

Arithmetic mean counts and efficacy

| Day | Control mean | Mean (Eff%) | p-value | Mean (Eff%) | p-value |
|---|--------------|--------------|---------|--------------|---------|
| Group | Group 1 | Group 2 | | Group 3 | |
| Day 2 | 59.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 9 | 67.8 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 16 | 69.5 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 23 | 71.8 | 0.8 (98.8%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 30 | 71.3 | 14.8 (79.2%) | < .0001 | 0.2 (99.8%) | < .0001 |
| Group 1: Negative control (untreated), shampooed on Days 9 and 23 | | | | | |
| Group 2: Dogs were treated with the IVP (Activyl®) and shampooed on Days 9 and 23 | | | | | |
| Group 3: Dogs were treated with the IVP (Activyl®) and not shampooed | | | | | |

Geometric mean counts and efficacy

| Day | Control mean | Mean (Eff%) | p-value | Mean (Eff%) | p-value |
|---|--------------|--------------|---------|--------------|---------|
| Group | Group 1 | Group 2 | | Group 3 | |
| Day 2 | 52.5 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 9 | 65.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 16 | 68.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 23 | 69.8 | 0.6 (99.1%) | < .0001 | 0.0 (100.0%) | < .0001 |
| Day 30 | 68.9 | 3.4 (95.0%) | 0.0006 | 0.1 (99.8%) | < .0001 |
| Group 1: Negative control (untreated), shampooed on Days 9 and 23 | | | | | |
| Group 2: Dogs were treated with the IVP (Activyl®) and shampooed on Days 9 and 23 | | | | | |
| Group 3: Dogs were treated with the IVP (Activyl®) and not shampooed | | | | | |

(4) Conclusion: based on the geometric mean, the study supports that shampooing with antibacterial shampoo twice starting 9 days after treatment does not affect the efficacy of the product against cat fleas.

(5) Is the study acceptable or not? The study is scientifically sound and acceptable.

Claim supported by MRID: "Remains effective against cat fleas after antibacterial shampoo treatment."

49314102. Fourie, J.J.. The Effect of Activyl®, an Indoxacarb Spot-On Treatment, Against Active Feeding of the Cat Flea (*Ctenocephalides felis*) on Dogs. Oct. 1, 2013.

(1) Not GLP

(2) Study Design (from the primary review):

Test Material(s):

Treatments followed the dose rates as set out below.

| IVP | Group | Weight range | Dose |
|------------------|-------|---------------|--------------|
| Activyl® spot-on | 2 | >1.8 – 6.6 kg | 0.51 ml tube |
| | | >6.6 – 10 kg | 0.77 ml tube |
| | | >10 – 20 kg | 1.54 ml tube |

List the treatments including untreated control (express application rate as g/m²):

Twelve healthy dogs, weighing 8.40 to 19.00 kg, were studied in this parallel group design, randomized, single center, non-blinded study. On Day -1, the 12 dogs included were ranked, within gender, in descending order of individual pre-treatment flea counts. Within each gender, animals were then blocked into six blocks of two dogs each. Within each block, dogs were randomly allocated to the two study groups: Group 1, untreated control and Group 2, treated with the IVP (on Day 0).

The animals were observed once daily for general health. Following treatment, animals from all groups were also observed approximately hourly for four hours for adverse reactions to treatment. Clinical and local tolerance observations and evaluation of cosmetic effects were conducted on all dogs prior to treatment, approximately 4 hours post-treatment and three and seven days after treatment. Hair was clipped to a length of approximately 5 mm, 6 days post-treatment to allow attachment of flea containment chambers.

On Day + 7, fleas were separated according to gender and infested on the dogs.

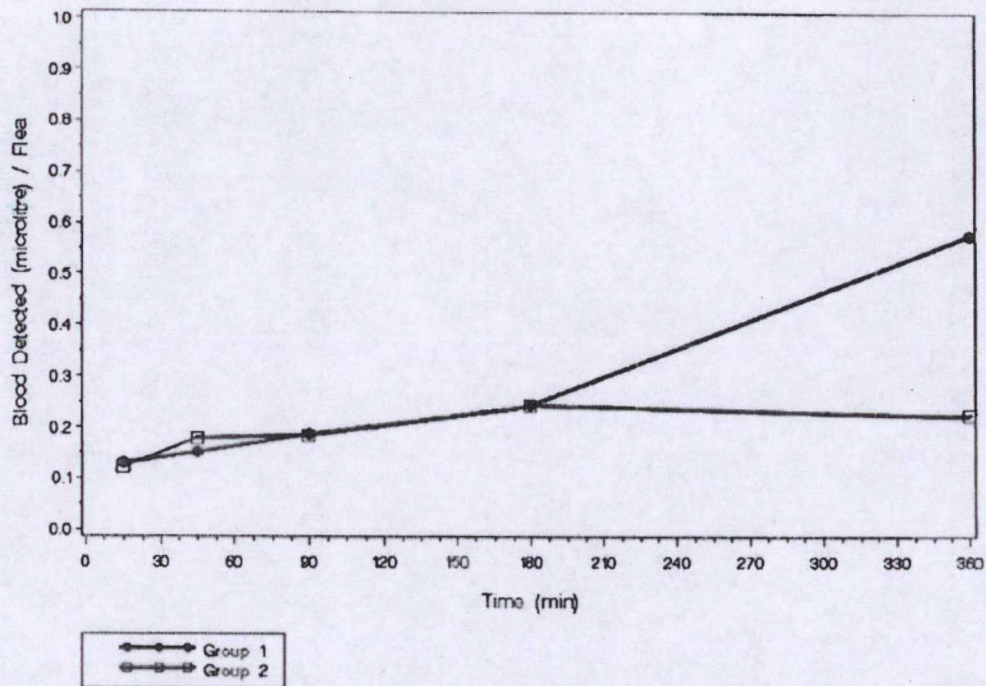
Ten plexiglass chambers (3.6 cm diameter) were attached to the back of each dog using contact adhesive. Flea infestations were performed by adding 15 male or female fleas (*Ctenocephalides felis* ClinVet USA strain) to each chamber to allow each dog to have five chambers with 15 males / chamber and 5 chambers with 15 females / chamber. Fleas and frass were collected from the chambers using vacuum aspiration at 15 min, 45 min, 90 min, 180 min and 360 min post infestation. Frass and fleas were analysed for the presence of hemoglobin using Drabkin's reagent.

(3) Results:

Blood Feeding Quantification:

The arithmetic mean of detected blood internalized by the fleas (male and female) as well as present in the frass for all time points and both groups were summarised in the table and graphs below. An average flea recovery rate of 90.67% (13.60/15 fleas) was obtained for each attached chamber using vacuum aspiration after infestation. Chamber failure (broken chamber, dislodged from attachment site) until vacuum aspiration was 9.17% (11/120 chambers). Similar active blood feeding was observed for fleas on the IVP treated dogs (Group 2) compared to fleas on untreated control dogs (Group 1) up to 180 min post infestation. No statistically significant ($p > 0.05$) difference in detectible blood feeding either internalized or present in frass was observed between the two study groups up to this time point (180 min). At 360 min, no increase in detectible blood from the previous assessment time point (180 min) was observed in either fleas or frass collected from the IVP treated dogs (Group 2). A marked increase in detectible blood was, however, observed for fleas on the untreated control dogs (Group 1) up to the 360 min assessment time point. Statistically significantly ($p < 0.05$) less detectible blood feeding between Groups 1 and 2 was detected at 360 min post infestation. Active blood feeding by fleas on the IVP treated dogs stopped at 180 min post infestation where 7.44% less blood either internalized or present in frass was detected when the 360 min sample was compared to the 180 min sample. In comparison, an increase of 137.25% in detectible blood was observed for the control group for the same timepoints (see statistical results, pg 141). Consequently a difference of 144.69% was observed in feeding of fleas on the control and IVP treated dogs from 180 to 360 min post infestation.

Blood Detected (microlitre) / Flea: Frass + Fleas
Mean Values

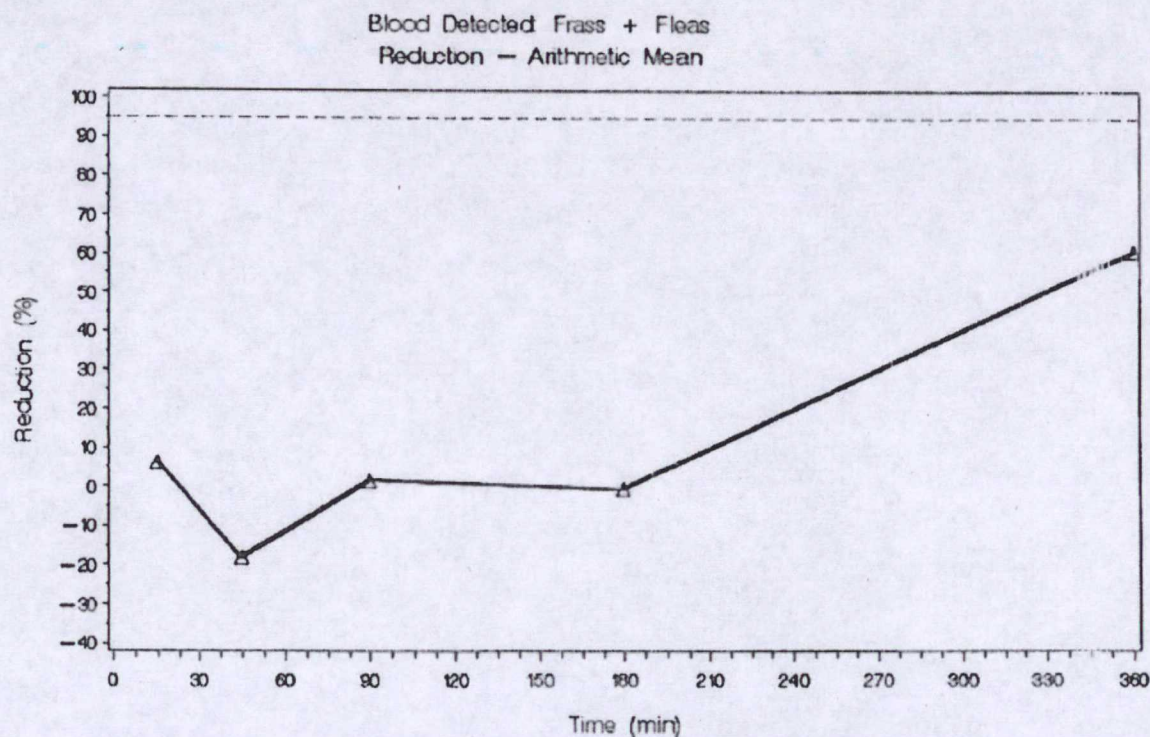


| Group | Time | Average blood detected (μl) / flea (in frass) | | | Average blood detected (μl) / flea (internalized) | | | Average blood detected (μl) / flea (frass + internalized) | | |
|---------|---------|---|---------------------|---------------------|---|--------|--------|---|---------------------|---------------------|
| | | Male | Female | All | Male | Female | All | Male | Female | All |
| Group 1 | 15 min | 0.0370 | 0.0296 | 0.0336 | 0.0755 | 0.1202 | 0.0958 | 0.1125 | 0.1497 | 0.1294 |
| Group 1 | 45 min | 0.0856 | 0.0872 | 0.0774 | 0.0628 | 0.0888 | 0.0743 | 0.1483 | 0.1560 | 0.1518 |
| Group 1 | 90 min | 0.1074 | 0.1146 | 0.1110 | 0.0451 | 0.1089 | 0.0770 | 0.1525 | 0.2235 | 0.1880 |
| Group 1 | 180 min | 0.1432 | 0.2234 | 0.1833 | 0.0499 | 0.0699 | 0.0599 | 0.1931 | 0.2933 | 0.2432 |
| Group 1 | 360 min | 0.4240 | 0.6455 | 0.5347 | 0.0312 | 0.0532 | 0.0422 | 0.4552 | 0.6987 | 0.5770 |
| Group 2 | 15 min | 0.0438 | 0.0294 | 0.0366 | 0.0636 | 0.1060 | 0.0848 | 0.1074 | 0.1355 | 0.1214 |
| Group 2 | 45 min | 0.0847 | 0.0874 | 0.0861 | 0.0549 | 0.1310 | 0.0930 | 0.1396 | 0.2184 | 0.1790 |
| Group 2 | 90 min | 0.1152 | 0.1134 | 0.1143 | 0.0478 | 0.0928 | 0.0703 | 0.1630 | 0.2063 | 0.1846 |
| Group 2 | 180 min | 0.1408 | 0.2261 | 0.1834 | 0.0374 | 0.0829 | 0.0602 | 0.1781 | 0.3090 | 0.2436 |
| Group 2 | 360 min | 0.1174 ¹ | 0.2306 ¹ | 0.1803 ¹ | 0.0384 | 0.0506 | 0.0452 | 0.1558 ¹ | 0.2812 ¹ | 0.2255 ¹ |

¹Group 2 differed statistically significantly ($p < 0.05$) from the untreated control Group 1

Reduction in Blood Feeding:

Feeding reduction relative to the control group indicated no statistically significant ($p>0.05$) reduction in detectable blood volumes during the first 180 min, but a statistically significant ($p<0.05$) reduction in feeding (60.9%) was observed at 360 min for both male and female fleas (see table and graph below).



Group 2

| Time | Reduction: Frass and Fleas (Male) | | | Reduction: Frass and Fleas (Female) | | | Reduction: Frass and Fleas (Male and Female combined) | | |
|---------|-----------------------------------|---------|----------------------------|-------------------------------------|---------|----------------------------|---|---------|----------------------------|
| | Group 1 | Group 2 | Reduction (%) ^a | Group 1 | Group 2 | Reduction (%) ^a | Group 1 | Group 2 | Reduction (%) ^a |
| 15 min | 0.1125 | 0.1074 | 4.6 | 0.1497 | 0.1355 | 9.5 | 0.1294 | 0.1214 | 6.1 |
| 45 min | 0.1483 | 0.1396 | 5.9 | 0.1560 | 0.2184 | -40.0 | 0.1518 | 0.1790 | -18.0 |
| 90 min | 0.1525 | 0.1630 | -6.8 | 0.2235 | 0.2063 | 7.7 | 0.1880 | 0.1846 | 1.1 |
| 180 min | 0.1931 | 0.1781 | 7.7 | 0.2933 | 0.3090 | -5.4 | 0.2432 | 0.2436 | -0.2 |
| 360 min | 0.4552 | 0.1558 | 65.8 | 0.6987 | 0.2812 | 59.8 | 0.5770 | 0.2255 | 60.9 |

^aBased on arithmetic means

(4) Conclusion:

The first and only infestation was done 7 days after treatment. Reduction in feeding was statistically significant over the control group by 360 min (6 hours) of the infestation, however was only reduced by 60.9% vs. the control. There was no statistical difference in feeding at the 180 min (3 hour) time frame.

(5) Is the study acceptable or not? The study is scientifically sound and acceptable.

Claim supported by MRID: "This product starts to reduce blood feeding of adult fleas on dogs starting 7 days and 6 hours after treatment is applied."

V. RECOMMENDATIONS:

(1) Labeling:

The following label claims are acceptable:

- Remains effective against cat fleas after antibacterial shampoo treatment
- This product starts to reduce blood feeding of adult fleas on dogs in 6 hours of exposure starting 7 days after treatment is applied.

The following label claims are unacceptable:

- Effective against Cat Flea feeding (within 3 hours)(following application)
- Stops cat flea feedings within 6 hours (following application)

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID 493491-02. Fourie, J.J., The Effect of Activyl®, an Indoxacarb Spot-On Treatment, Against Active Feeding of the Cat Flea (*Ctenocephalides felis*) on Dogs. Oct. 1, 2013.

OCSPP 810.3300: Treatments to Control Pests of Humans and Pets

Product Name: Activyl® for Dogs and Puppies

EPA Reg. No. or File Symbol: 773-94

Decision number: 491741

DP number: 420896

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No.: 2-215

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: Dennis M. Opresko
Date: 07/21/2014

Secondary Reviewers:
Gene Burgess, Ph.D.

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Date: 07/21/2014

Robert H. Ross, M.S. Program Manager

Signature: Robert H. Ross
Date: 07/21/2014

Quality Assurance:
Angela M. Edmonds, B.S.

Signature: Angela M. Edmonds
Date: 07/21/2014

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.
Summitec Corp. for the U.S. Environmental Protection Agency under Contract No. EP-W-11-014

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE: OCSPP 810.3300: Treatments to Control Pests of Humans and Pets

MRID: **493141-02.** Fourie, J.J.. The Effect of Activyl®, an Indoxacarb Spot-On Treatment, Against Active Feeding of the Cat Flea (*Ctenocephalides felis*) on Dogs. Oct. 1, 2013.

DP BARCODE: 420896

DECISION NO: 491741

SUBMISSION NO: 953017

SPONSOR: Intervet, Inc.
(d/b/a Merck Animal Health)
556 Morris Avenue
Summit, New Jersey 07901

TESTING FACILITY: ClinVet International (Pty) Ltd
Uitzich Road
Bainsvlei
Bloemfontein
Republic of South Africa

STUDY DIRECTOR: Not reported

SUBMITTER: Micah T. Reynolds,
Regulatory Consultant to Intervet, Inc.
Technology Sciences Group, Inc.

STUDY COMPLETED: 01/10/2013

CONFIDENTIALITY CLAIMS: None

GOOD LABORATORY PRACTICE: This study was not conducted in accordance with Good Laboratory Practices standards as defined in the requirements of 40 CFR Part 160, however adhered to the principles of Good Clinical Practices (VICH GL 9, June 2000).

TEST MATERIAL:

PRODUCT NAME: Activyl® for Dogs and Puppies
EPA REGISTRATION NUMBER OR FILE SYMBOL:
773-94

ACTIVE INGREDIENT NAME: Indoxacarb

CHEMICAL NAME:

(S)-methyl 7-chloro-2,5-dihydro-2-[[[(methoxycarbonyl)[4-trifluoromethoxy]phenyl]amino]-
-carbonyl]indeno[1,2-c][1,3,4]oxadiazine-4a(3H)-carboxylate.....

A.I. %: 19.53%

PC CODE: 067710

CAS NO.: Not given

FORMULATION TYPE: Spot-on

PRODUCT APPLICATION RATE(S):

| | |
|---------------------------|--|
| For 0.51 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than |
| For 0.77 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than |
| For 1.54 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than |
| For 3.08 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than |
| For 4.62 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than |

ACTIVE INGREDIENT APPLICATION RATE(S): Not
given.

**PROPOSED LABEL
MARKETING CLAIMS:**

33. Efficient against Cat Flea (*Ctenocephalides felis*) (*C. felis*) feeding (within 3 hours) (following application)

34. (Alt: rate or brand name) (This product) stops cat flea feedings within 16 (six) hours (following application)

35. (Alt: rate or brand name) (This product) remains effective against cat fleas after antibacterial shampoo treatment

STUDY REVIEW

Purpose: The objective of the study was to evaluate the effect of Activyl® on the blood feeding behavior of *Ctenocephalides felis* on dogs.

MATERIALS AND METHODS

Test Location: Bainsvlei, Bloemfontein. Republic of South Africa (location of testing laboratory).

Test Material(s): Indoxacarb (195 mg/mL (19.53%)); same as labeled product.

Test Species Name, Life Stage, Sex and Age: Adult unfed cat fleas, *Ctenocephalides felis*; mixed sex.

Describe test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Twelve healthy dogs, weighing 8.40 to 19.00 kg, were studied in this parallel group design, randomized, single center, non-blinded study. On Day -1, the 12 dogs included were ranked, within gender, in descending order of individual pre-treatment flea counts. Within each gender, animals were then blocked into six blocks of two dogs each. Within each block, dogs were randomly allocated to the two study groups: Group 1, untreated control and Group 2, treated with the IVP (on Day 0).

The animals were observed once daily for general health. Following treatment, animals from all groups were also observed approximately hourly for four hours for adverse reactions to treatment. Clinical and local tolerance observations and evaluation of cosmetic effects were conducted on all dogs prior to treatment, approximately 4 hours post-treatment and three and seven days after treatment. Hair was clipped to a length of approximately 5 mm, 6 days post-treatment to allow attachment of flea containment chambers.

On Day + 7, fleas were separated according to gender and infested on the dogs.

Ten plexiglass chambers (3.6 cm diameter) were attached to the back of each dog using contact adhesive. Flea infestations were performed by adding 15 male or female fleas (*Ctenocephalides felis* ClinVet USA strain) to each chamber to allow each dog to have five chambers with 15 males / chamber and 5 chambers with 15 females / chamber. Fleas and frass were collected from the chambers using vacuum aspiration at 15 min, 45 min, 90 min, 180 min and 360 min post infestation. Frass and fleas were analysed for the presence of hemoglobin using Drabkin's reagent.

List the treatments including untreated control (express application rate as g/m²):

Treatments followed the dose rates as set out below.

| IVP | Group | Weight range | Dose |
|------------------|-------|---------------|--------------|
| Activyl® spot-on | 2 | >1.8 – 6.6 kg | 0.51 ml tube |
| | | >6.6 – 10 kg | 0.77 ml tube |
| | | >10 – 20 kg | 1.54 ml tube |

The volume of the IVP administered to the dogs, are given below:

| GROUP 2: IVP Day 0 (Activyl® spot-on) | | |
|---------------------------------------|-------|------|
| ID | BW | IVP |
| DF7 C6D | 16.60 | 1.54 |
| EA0 FEE | 18.40 | 1.54 |
| 95A 4CA | 15.40 | 1.54 |
| E9F D35 | 18.60 | 1.54 |
| E18 F40 | 19.00 | 1.54 |
| CCF 84E | 8.40 | 0.77 |
| Arithmetic mean | 16.07 | 1.41 |

ID = animal identification; BW = body weight (kg); IVP (Investigational Veterinary Product) = volume (mL) of IVP administered

The label directions for Activyl® for Dogs and Puppies are as follows:

| | |
|---------------------------|---|
| For 0.51 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 4 lb. |
| For 0.77 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 14 lb. |
| For 1.54 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 22 lb. |
| For 3.08 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 44 lb. |
| For 4.62 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 88 lb. |

The applications rates used in the study correspond to the label-recommended application rates.

Number of replicates per treatment: Six dogs per group.

Number of individuals per replicate: 15 fleas per chamber; 5 chambers per dog.

Length of exposure to treatment (time in seconds, minutes or hours): Single application of test product.

Were tested specimens transferred to clean containers? N/A.

Experimental conditions (state relative humidity, temperature, and photoperiod):

The temperatures recorded in the cage environment ranged from 19.7°C to 23.1°C in unit 20 room B.

The relative humidity recorded in the cage environment ranged from 32.9% to 66.4% in unit 20 room B.

Data or endpoints collected/recorded:

The data were listed and described per time point for the following scenarios, after the calculation of the variable average blood detected per flea (dividing the amount of blood detected by the applicable number of fleas counted):

1. Frass per gender
2. Frass for both genders combined
3. Fleas per gender
4. Fleas for both genders combined
5. Sum of frass and fleas per gender
6. Sum of frass and fleas for both genders combined

The following descriptive statistics were provided: mean, minimum, maximum, standard deviation, CV%, geometric mean and median for each scenario.

Data analysis:

The quantitative data from the Drabkin's assay was compared between the two study groups. SAS Version 9.3 TS Level 1M2 were used for all the statistical analyses.

For each scenario above (and per time point), the average blood detected per flea in the untreated control group (Group 1) and the IVP group (Group 2) was compared using an analysis of variance (ANOVA) with treatment effect on untransformed values utilizing PROC GLM of SAS. In addition, the groups were compared by a non-parametric analysis using the Mann-Whitney test on untransformed values utilizing PROC NPAR1WAY of SAS.

For scenario 5 and 6 (section 18.2.1), the % reduction (difference between the two groups as percentage of the untreated control group) per time point was calculated as below and tabulated:

Reduction (%) = $100 \times (M_c - M_t) / M_c$, where

M_c = arithmetic or geometric mean of blood detected /flea for subjects in the untreated control group (Group 1).

M_t = arithmetic or geometric mean of blood detected /flea for subjects in the IVP group (Group 2)

For scenario 6 above, time points were inspected for significant differences between the groups and inspected further as follows:

Within a group, the change from 180 min to 360 min was calculated and presented as percentage of 180 min. The difference in this percentage change between the groups was tabulated. This was done for scenario 5 and 6 above.

The level of significance of the formal tests are set at 5%, all tests were two sided.

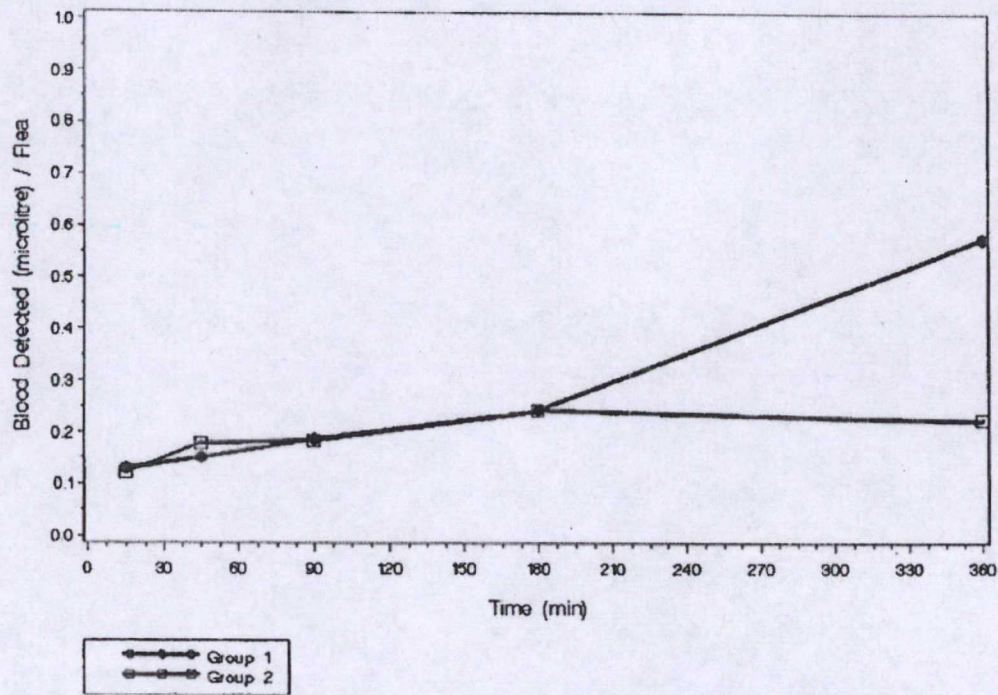
RESULTS

Raw data (flea counts) for each dog, and a copy of the test protocol were not included in the study report. The statistical analyses of the results were included in Appendix B of the study report. No serious adverse health effects related to the test product were reported. Study Plan Deviations are summarized in the Appendix to this DER.

Blood Feeding Quantification:

The arithmetic mean of detected blood internalized by the fleas (male and female) as well as present in the frass for all time points and both groups were summarised in the table and graphs below. An average flea recovery rate of 90.67% (13.60/15 fleas) was obtained for each attached chamber using vacuum aspiration after infestation. Chamber failure (broken chamber, dislodged from attachment site) until vacuum aspiration was 9.17% (11/120 chambers). Similar active blood feeding was observed for fleas on the IVP treated dogs (Group 2) compared to fleas on untreated control dogs (Group 1) up to 180 min post infestation. No statistically significant ($p > 0.05$) difference in detectible blood feeding either internalized or present in frass was observed between the two study groups up to this time point (180 min). At 360 min, no increase in detectible blood from the previous assessment time point (180 min) was observed in either fleas or frass collected from the IVP treated dogs (Group 2). A marked increase in detectible blood was, however, observed for fleas on the untreated control dogs (Group 1) up to the 360 min assessment time point. Statistically significantly ($p < 0.05$) less detectible blood feeding between Groups 1 and 2 was detected at 360 min post infestation. Active blood feeding by fleas on the IVP treated dogs stopped at 180 min post infestation where 7.44% less blood either internalized or present in frass was detected when the 360 min sample was compared to the 180 min sample. In comparison, an increase of 137.25% in detectible blood was observed for the control group for the same timepoints (see statistical results, pg 141). Consequently a difference of 144.69% was observed in feeding of fleas on the control and IVP treated dogs from 180 to 360 min post infestation.

Blood Detected (microlitre) / Flea: Frass + Fleas
Mean Values



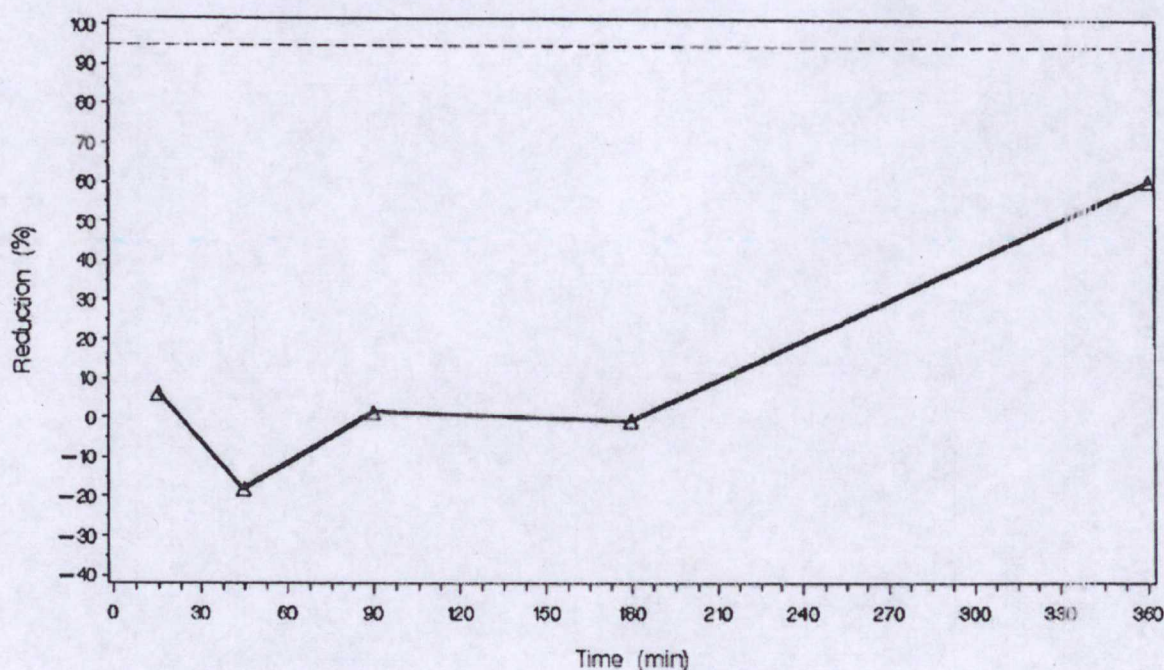
| Group | Time | Average blood detected (μl) / flea (in frass) | | | Average blood detected (μl) / flea (internalized) | | | Average blood detected (μl) / flea (frass + internalized) | | |
|---------|---------|---|---------------------|---------------------|---|--------|--------|---|---------------------|---------------------|
| | | Male | Female | All | Male | Female | All | Male | Female | All |
| Group 1 | 15 min | 0.0370 | 0.0298 | 0.0336 | 0.0755 | 0.1202 | 0.0958 | 0.1125 | 0.1497 | 0.1294 |
| Group 1 | 45 min | 0.0856 | 0.0672 | 0.0774 | 0.0628 | 0.0888 | 0.0743 | 0.1483 | 0.1560 | 0.1518 |
| Group 1 | 90 min | 0.1074 | 0.1148 | 0.1110 | 0.0451 | 0.1089 | 0.0770 | 0.1625 | 0.2235 | 0.1880 |
| Group 1 | 180 min | 0.1432 | 0.2234 | 0.1833 | 0.0499 | 0.0699 | 0.0599 | 0.1931 | 0.2933 | 0.2432 |
| Group 1 | 360 min | 0.4240 | 0.6455 | 0.5347 | 0.0312 | 0.0532 | 0.0422 | 0.4552 | 0.6987 | 0.5770 |
| Group 2 | 15 min | 0.0438 | 0.0294 | 0.0366 | 0.0636 | 0.1060 | 0.0848 | 0.1074 | 0.1355 | 0.1214 |
| Group 2 | 45 min | 0.0847 | 0.0874 | 0.0861 | 0.0549 | 0.1310 | 0.0930 | 0.1396 | 0.2184 | 0.1790 |
| Group 2 | 90 min | 0.1152 | 0.1134 | 0.1143 | 0.0478 | 0.0928 | 0.0703 | 0.1630 | 0.2063 | 0.1846 |
| Group 2 | 180 min | 0.1408 | 0.2261 | 0.1834 | 0.0374 | 0.0829 | 0.0602 | 0.1781 | 0.3090 | 0.2436 |
| Group 2 | 360 min | 0.1174 ¹ | 0.2306 ¹ | 0.1803 ¹ | 0.0384 | 0.0506 | 0.0452 | 0.1558 ¹ | 0.2812 ¹ | 0.2255 ¹ |

¹Group 2 differed statistically significantly ($p < 0.05$) from the untreated control Group 1

Reduction in Blood Feeding:

Feeding reduction relative to the control group indicated no statistically significant ($p > 0.05$) reduction in detectable blood volumes during the first 180 min, but a statistically significant ($p < 0.05$) reduction in feeding (60.9%) was observed at 360 min for both male and female fleas (see table and graph below).

Blood Detected Frass + Fleas
Reduction — Arithmetic Mean



Group 2

| Time | Reduction: Frass and Fleas (Male) | | | Reduction: Frass and Fleas (Female) | | | Reduction: Frass and Fleas (Male and Female combined) | | |
|---------|-----------------------------------|---------|----------------------------|-------------------------------------|---------|----------------------------|---|---------|----------------------------|
| | Group 1 | Group 2 | Reduction (%) ^a | Group 1 | Group 2 | Reduction (%) ^a | Group 1 | Group 2 | Reduction (%) ^a |
| 15 min | 0.1125 | 0.1074 | 4.6 | 0.1497 | 0.1355 | 9.5 | 0.1294 | 0.1214 | 12 |
| 45 min | 0.1483 | 0.1396 | 5.9 | 0.1560 | 0.2184 | -40.0 | 0.1518 | 0.1790 | -18.0 |
| 90 min | 0.1525 | 0.1630 | -6.8 | 0.2235 | 0.2063 | 7.7 | 0.1880 | 0.1846 | 8 |
| 180 min | 0.1931 | 0.1781 | 7.7 | 0.2933 | 0.3090 | -5.4 | 0.2432 | 0.2436 | -0.2 |
| 360 min | 0.4552 | 0.1558 | 65.8 | 0.6987 | 0.2812 | 59.8 | 0.5770 | 0.2255 | 60.9 |

^aBased on arithmetic means

Study Author's Conclusions

The IVP (Activyl®) stopped active flea feeding beginning 3 hours after exposure resulting in a significant reduction (60.9%) in blood feeding within 6 hours post exposure. No active feeding (7.44% decrease in detectible blood) could be detected from 3 hours to 6 hours post exposure for the IVP treated group, whereas a significant increase in feeding (137.25% increase in detectible blood) was detected for the control group over the same period.

Reviewer's Conclusions

The study results support the conclusions of the study author in that the product began to stop flea feeding after 3 hours when compared to controls. The study author states that the 7.44% decrease in detectible blood in fleas and frass at 6 hours indicates no active flea feeding; however, this might have been more clearly documented if a third test group had been used in which the fleas had been removed from the dogs at 3 hours and then the blood in the fleas and frass had been measured at 6 hours and compared to the group remaining on the dogs for 6 hours.

NOTE: Guideline 810-3300 states the following:

1) *All testing shall be conducted on male and female adult dogs of various sizes and hair lengths.* Five of the six animals used in the treated group in the study were within a single size range.

APPENDIX
STUDY PLAN AMENDMENTS AND DEVIATIONS

| | |
|------------------------------|---|
| Amendment #1 | Effective date: 06 March 2013 |
| | a) The pre-treatment flea infestations and counts scheduled for Days -8/-4 were conducted on Days -4/-2 instead (sections 8.2, 8.3, 17.3.1 and 17.3.2). |
| | b) Blood was collected from all dogs on Day -6, instead of Day -7 as stated in the study protocol (sections 8.2 and 17.1.6) |
| Reason for changes: | Logistical reasons |
| Impact on study: | No negative impact |
| Amendment #2 | Effective date: 07 June 2013 |
| | A qPCR was not conducted on collected fleas to assess blood ingestion as described in the protocol section 17.3.5, instead the specific reaction between haemoglobin and Drabkin's reagent were used to quantify the volume of blood ingested by fleas. |
| Reason for changes: | Requested by study sponsor |
| Impact on study: | No negative impact, flea feeding was still quantified |
| Deviation #1 | Effective date: 16 September 2013 |
| | Incorrect IVP dose weight ranges were indicated in the protocol section 14.1.2 (Dose weight ranges: 1.8 – 6.36 kg; >6.36 – 10 kg; >10 -20 kg) and differed from dose weight ranges indicated on IVP labels (Dose weight ranges: 1.8 – 6.6 kg; >6.6 – 10 kg; >10 – 20 kg). The label recommended dose weight ranges were used. |
| Reason for deviation: | Incorrect IVP dose weight ranges were indicated in the protocol. |
| Impact on study: | None. The label recommended dose weight ranges were used. |

TASK 2 DATA EVALUATION RECORD

STUDY TYPE: Product Performance

MRID 493491-01. Liebenberg, J.E., Impact of Antibacterial Shampooing on the Efficacy of Activyl® (Indoxacarb) Topical Treatment against Cat Flea (*Ctenocephalides felis*) Infestations on Dogs under Laboratory Conditions. Dec. 13, 2013.

OCSPP 810.3300: Treatments to Control Pests of Humans and Pets

Product Name: Activyl® for Dogs and Puppies

EPA Reg. No. or File Symbol: 773-94

Decision number: 491741

DP number: 420896

Prepared for
Registration Division (7505)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, DC 20460

Prepared by
Summitec Corporation
Task Order No.: 2-215

Primary Reviewer:
Dennis M. Opresko, Ph.D.

Signature: Dennis M. Opresko ^{AL}
Date: 07/21/2014

Secondary Reviewers:
Gene Burgess, Ph.D.

Signature: Gene Burgess ^{HE}
Date: 07/21/2014

Robert H. Ross, M.S. Program Manager

Signature: Robert H. Ross ^{HB}
Date: 07/21/2014

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Angela M. Edmonds, B.S.

Signature: Angela M. Edmonds ^{AE}
Date: 07/21/2014

Disclaimer

This review may have been altered subsequent to the contractors' signatures above.
Summitec Corp. for the U.S. Environmental Protection Agency under Contract No. EP-W-11-014

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

STUDY TYPE: OCSPP 810.3300: Treatments to Control Pests of Humans and Pets

MRID: 49349101. Liebenberg, J.E., Impact of Antibacterial Shampooing on the Efficacy of Activyl® (Indoxacarb) Topical Treatment against Cat Flea (*Ctenocephalides felis*) Infestations on Dogs under Laboratory Conditions. Dec. 13, 2013.

DP BARCODE: 420896

DECISION NO: 491741

SUBMISSION NO: 953017

SPONSOR: Intervet, Inc.
(d/b/a Merck Animal Health)
556 Morris Avenue
Summit, New Jersey 07901

TESTING FACILITY: ClinVet International (Pty) Ltd
Uitzich Road
Bainsvlei
Bloemfontein
Republic of South Africa

STUDY DIRECTOR: Not reported

SUBMITTER: Micah T. Reynolds,
Regulatory Consultant to Intervet, Inc.
Technology Sciences Group, Inc.

STUDY COMPLETED: 13/12/2013

CONFIDENTIALITY CLAIMS: None

GOOD LABORATORY PRACTICE: This study was not conducted in accordance with Good Laboratory Practices standards as defined in the requirements of 40 CFR Part 160, however adhered to the principles of Good Clinical Practices (VICH GL 9, June 2000).

DATA EVALUATION RECORD

[EPA Primary Reviewer's Name]

| | |
|----------------------------------|---|
| STUDY TYPE: | OCSP 810.3300: Treatments to Control Pests of Humans and Pets |
| MRID: | 493141-01. Liebenberg, J.E., Impact of Antibacterial Shampooing on the Efficacy of Activyl® (Indoxacarb) Topical Treatment against Cat Flea (<i>Ctenocephalides felis</i>) Infestations on Dogs under Laboratory Conditions. Dec. 13, 2013. |
| DP BARCODE: | 420896 |
| DECISION NO: | 491741 |
| SUBMISSION NO: | 953017 |
| SPONSOR: | Intervet, Inc. (d/b/a Merck Animal Health) 556 Morris Avenue Summit, New Jersey 07901 |
| TESTING FACILITY: | ClinVet International (Pty) Ltd Uitzich Road Bainsvlei Bloemfontein Republic of South Africa |
| STUDY DIRECTOR: | Not reported |
| SUBMITTER: | Micah T. Reynolds, Regulatory Consultant to Intervet, Inc. Technology Sciences Group, Inc. |
| STUDY COMPLETED: | 13/12/2013 |
| CONFIDENTIALITY CLAIMS: | None |
| GOOD LABORATORY PRACTICE: | This study was not conducted in accordance with Good Laboratory Practices standards as defined in the requirements of 40 CFR Part 160, however adhered to the principles of Good Clinical Practices (VICH GL 9, June 2000). |

TEST MATERIAL:

PRODUCT NAME: Activyl® for Dogs and Puppies
EPA REGISTRATION NUMBER OR FILE SYMBOL:
773-94

ACTIVE INGREDIENT NAME: Indoxacarb

CHEMICAL NAME:

(S)-methyl 7-chloro-2,5-dihydro-2-[[[(methoxycarbonyl)[4-trifluoromethoxy]phenyl]amino]-carbonyl]indeno[1,2-c][1,3,4]oxadiazine-4a(3H)-carboxylate.....

A.I. %: 19.53%.

PC CODE: 067710

CAS NO.: Not given

FORMULATION TYPE: Spot-on

PRODUCT APPLICATION RATE(S):

| | |
|----------------------------|---|
| For 0.51 ml. package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 4 lb. |
| For 0.77 ml. package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 14 lb. |
| For 1.54 ml. package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 22 lb. |
| For 3.08 ml. package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 44 lb. |
| For 4.62 ml. package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 88 lb. |

ACTIVE INGREDIENT APPLICATION RATE(S): Not given.

**PROPOSED LABEL
MARKETING CLAIMS:**

Starts killing fleas within 8 hours... Protects... for 4 weeks.

13. Efficacy against Cat Flea (*Ctenocephalides felis*) (C. felis) feeding (within 3 hours) (following application)

14. Alt. (rate or brand name) (This product) stops cat flea feedings within (6) (six) hours (following application)

15. Alt. (rate or brand name) (This product) remains effective against cat fleas after antibacterial shampoo treatment

STUDY REVIEW

Purpose: The objective of the study was to evaluate the impact of antibacterial shampoo baths on the persistent efficacy of Activyl® applied topically at the commercially recommended dose (greater than 15 mg/kg body weight) to control fleas on dogs.

MATERIALS AND METHODS

Test Location: Bainsvlei, Bloemfontein. Republic of South Africa (location of testing laboratory).

Test Material(s): Indoxacarb (195 mg/mL (19.53%); same as labeled product.

Test Species Name, Life Stage, Sex and Age: Adult unfed cat fleas, *Ctenocephalides felis*; mixed sex.

Describe test containers, chambers and/or apparatus (include site description and location) and how experiment was conducted: Eighteen healthy, mongrel dogs, weighing 8.50 kg to 21.03 kg on Day -2, were studied in this parallel group design, randomized, single center, blinded, and controlled efficacy study. On Day -2, the 18 dogs included were ranked within gender in descending order of individual pretreatment live flea counts and subsequently grouped into blocks of three dogs each: Group 1, negative control; Group 2, IVP treated (Activyl® on Day 0) and shampooed on Days 9 and 23; and Group 3, IVP treated (Activyl® on Day 0), but not shampooed.

Hair lengths on the dogs averaged 19.79 mm in Group 1, 21.92 mm in Group 2, and 18.33 mm in Group 3.

Following administration, animals from all groups were observed approximately hourly for four hours for adverse reactions to treatment.

Flea infestations were performed with 100 adult, unfed *Ctenocephalides felis* (European origin) placed on each dog on Day -2 and then weekly from Days 7 to 28. Fleas were removed and counted 48± 2 hours post-infestation except for Day -2 infestation where the assessment was performed on Day 2.

Assessments were conducted according to the schedule below:

| Acclimatisation | Ranking and allocation to groups | IVP administration |
|-----------------|----------------------------------|--------------------|
| Days -7 to -1 | Day -2 | Day 0 |

| Shampooing (Group 1 and 2 only) | Flea infestations | Flea counts and removal ¹ |
|---------------------------------|-------------------------------|--------------------------------------|
| Days 9 and 23 | Days -7, -2, 7, 14, 21 and 28 | Days -5, 2, 9, 16, 23 and 30 |

¹ Flea counts were conducted 48 ± 2 hours post-IVP administration or flea infestations

List the treatments including untreated control (express application rate as g/m²):

Treatments followed the dose rates as set out below.

| Study groups | Sample size | Treatment | Active ingredient | Weight range | Dose |
|--------------|-------------|-----------|-------------------|--------------------|---------|
| 2 & 3 | 6 | Activyl® | Indoxacarb | > 6.6 kg to 10 kg | 0.77 mL |
| | | | | > 10.1 kg to 20 kg | 1.54 mL |
| | | | | > 20.1 kg to 40 kg | 3.08 mL |

The volume of the IVP administered to the dogs, are given below:

| GROUP 2: IVP (Activyl®, Shampooed) | | | GROUP 3: IVP (Activyl®, Not shampooed) | | |
|------------------------------------|-------|------|--|-------|------|
| ID | BW | IVP | ID | BW | IVP |
| 289 C76 | 9.93 | 0.77 | 6DC 064 | 17.14 | 1.54 |
| DF5 BFC | 21.03 | 3.08 | CD5 A9C | 16.23 | 1.54 |
| 4F5 FE1 | 11.26 | 1.54 | 4F6 65B | 11.51 | 1.54 |
| 4F2 04E | 13.05 | 1.54 | CD3 D1D | 14.66 | 1.54 |
| 267 3AD | 14.35 | 1.54 | DF6 232 | 17.74 | 1.54 |
| 284 D12 | 8.50 | 0.77 | CC3 ADA | 19.29 | 1.54 |
| Arithmetic mean | 13.02 | 1.54 | Arithmetic mean | 16.10 | 1.54 |

ID = identification; BW = body weight (kg); IVP = volume (mL) of IVP administered

The label directions for Activyl® for Dogs and Puppies are as follows:

| | |
|---------------------------|---|
| For 0.51 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 4 lb. |
| For 0.77 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 14 lb. |
| For 1.54 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 22 lb. |
| For 3.08 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 44 lb. |
| For 4.62 mL package size: | Do not use on dogs and puppies under 8 weeks of age and weighing less than 88 lb. |

The applications rates used in the study correspond to the label application rates.

Number of replicates per treatment: Six dogs per group.

Number of individuals per replicate: 100 fleas per dog on Days -2, 7, 14, 21, and 28.

Length of exposure to treatment (time in seconds, minutes or hours): Single application of test product.

Were tested specimens transferred to clean containers? N/A.

Experimental conditions (state relative humidity, temperature, and photoperiod):

The temperatures recorded in the kennel environment ranged from 14.0°C to 26.5°C in section A and from 13.4°C to 24.9°C in section D of unit 5.

Relative humidity recorded in the kennel environment ranged from 23.7% to 63.0% in section A and from 11.9% to 72.0% in section D of unit 5.

Data or endpoints collected/recorded:

The efficacy against fleas were calculated for the treatment group at each assessment day according to the formulas given below. Efficacy calculations were based on arithmetic means, but geometric means were presented and analysed as supportive evidence. Geometric means were calculated using the flea (count + 1) data and one (1) was subsequently subtracted from the result to obtain a meaningful value for the geometric mean of each group.

Efficacy (%) = $100 \times (M_c - M_t) / M_c$, where:

M_c = arithmetic or geometric mean of live fleas on the negative control group (Group 1)

M_t = arithmetic or geometric mean of live fleas on the treated group (Groups 2 or 3)

Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) on flea counts for the various assessment days and per group were calculated.

Data analysis:

As primary comparison, the groups were compared using an ANOVA (Proc GLM procedure in SAS) with a treatment effect on untransformed flea data. In addition, the groups were compared using an ANOVA (Proc GLM procedure in SAS) with a treatment effect after a logarithmic transformation on flea (count + 1) data.

SAS Version 9.3 TS Level 1M2 was used for all the statistical analyses.

RESULTS

A copy of the test protocol (Appendix D) and the statistical analyses of the results (Appendix A) were included in the study report. Raw data (flea counts) for each dog were not reported. No serious adverse health effects related to the test product were reported. Study Plan Deviations are summarized in the Appendix to this DER.

The arithmetic mean flea counts and efficacies based on these are summarised in the table below. The mean flea counts recorded for the untreated control group ranged from 59.2 to 71.8, indicating a vigorous challenge on all post-treatment assessment days. The Activyl® treated groups 2 (shampooed on Days 9 and 23) and 3 (not shampooed) differed statistically significantly ($p < 0.05$) from the untreated control group on all post-treatment assessment days. The mean flea counts did not differ statistically significantly ($p > 0.05$) between the shampooed not shampooed treated groups 2 and 3. The IVP (Activyl®) was effective ($> 95\%$) against fleas throughout the study when not shampooed, and effective ($> 95\%$) up to Day 23 with efficacy dropping to 79.2% on Day 30 in the shampooed group 2.

| Day | Control mean | Mean (Eff%) | p-value | Mean (Eff%) | p-value |
|---|--------------|--------------|---------|--------------|---------|
| Group | Group 1 | Group 2 | | Group 3 | |
| Day 2 | 59.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 9 | 67.8 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 16 | 69.5 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 23 | 71.8 | 0.8 (99.8%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 30 | 71.3 | 14.8 (79.2%) | < .0001 | 0.2 (99.8%) | <.0001 |
| Group 1: Negative control (untreated), shampooed on Days 9 and 23 | | | | | |
| Group 2: Dogs were treated with the IVP (Activyl®) and shampooed on Days 9 and 23 | | | | | |
| Group 3: Dogs were treated with the IVP (Activyl®) and not shampooed | | | | | |

The geometric mean flea counts and efficacies based on these are summarised in the table below. Based on geometric mean flea counts, both the shampooed and not-shampooed groups were effective ($> 95\%$) against fleas throughout the study.

| Day | Control mean | Mean (Eff%) | p-value | Mean (Eff%) | p-value |
|---|--------------|--------------|---------|--------------|---------|
| Group | Group 1 | Group 2 | | Group 3 | |
| Day 2 | 52.5 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 9 | 65.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 16 | 68.2 | 0.0 (100.0%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 23 | 69.8 | 0.6 (99.1%) | < .0001 | 0.0 (100.0%) | <.0001 |
| Day 30 | 68.9 | 3.4 (95.0%) | 0.0006 | 0.1 (99.8%) | <.0001 |
| Group 1: Negative control (untreated), shampooed on Days 9 and 23 | | | | | |
| Group 2: Dogs were treated with the IVP (Activyl®) and shampooed on Days 9 and 23 | | | | | |
| Group 3: Dogs were treated with the IVP (Activyl®) and not shampooed | | | | | |

Study Author's Conclusions

The bi-weekly shampooing of dogs with KetoChlor shampoo did not have a significant influence on the efficacy of Activyl® against *C. felis* for up to one month post-treatment when administered at label recommended doses.

Reviewer's Conclusions

The study results support the conclusions of the study author. Based on geometric means, the product was effective against fleas with or without twice weekly shampooing for up to 30 days. Based on arithmetic means, the product was effective for up to 23 days after twice weekly shampooing.

**APPENDIX
STUDY PLAN DEVIATIONS**

Deviation #1: Date of first deviation 06 October 2013, to the effect that the temperatures recorded in the rooms housing the dogs deviated from the protocol specified range ($20^{\circ}\text{C} \pm 4^{\circ}\text{C}$) by up to 0.6°C for short periods of time.

Reason for deviation: Air conditioning unit malfunction

Impact on study: No impact